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(54) DEPOT MEDICAMENTS IN CAPSULE FORM

(71) We, R. P. SCHERER, GmbH, a Company organized under German Law, of Eberbach/Baden, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Depot medicaments (i.e. in sustained release dosage form), especially those for oral administration, have become increasingly important in recent years. Their purpose is to administer the medicament to the patient in one or two single doses per day and to ensure in a simple manner a constant level of medicament in the blood. Oral depot medicaments and processes have been described, *inter alia*, in Pharm.Ind, 21, p. 298 [1959], Deutsche Apoth.Ztg. 99, p. 1175 [1959], Archiv d.Pharm. 293, p. 766 [1960], Deutsche Apoth. Ztg. 104, p. 797 [1964] and in German Patent Specifications. 1,076,329, 1,123,437 and 1,201,950.

The known shaped depot medicaments are tablets, coated tablets or hard gelatin capsules, but depot medicaments in soft gelatin capsules have not been known hitherto; this is due to the fact that soft gelatin capsules are filled with liquid or at least flowable substances, whereas the known depot medicaments are almost exclusively solid preparations that cannot be filled into soft gelatin capsules.

The present invention provides a gelatin capsule containing a depot medicament, the depot medicament comprising a solution or suspension, which solution or suspension is liquid or flowable at room temperature, of one or more physiologically active substances ane one or more substances selected from physiologically inert natural substances and physiologically inert synthetic substances, which physiologically inert substances are also inert to gelatin and are insoluble or only gradually soluble in water or in the juice of the gastro-intestinal tract in a liquid vehicle, which comprises a liquid water-miscible substance and/or a liquid mixture of a water-immiscible substance with a water-oil emulsifier or an auxiliary solvent, each of the physiologically inert natural or synthetic substances being such that, together with the liquid vehicle, it forms a microporous spongy body when it comes into contact with water or with the juice of the gastro-intestinal tract. The depot medicaments may be obtained by dissolving or suspending the active substance(s) together with the physiologically inert substance(s), which inert substance(s) is/are insoluble or only gradually soluble in water or in the juices of the gastro-intestinal tract, in the liquid vehicle and charging the liquid or flowable mixture into the capsules which may consist of soft or hard gelatin. In the case of flowable mixtures they may be liquid pastes at room temperature (about 18 to 27°C).

When the capsule filling comes into contact with water or with the juices of the gastro-intestinal tract a microporous, spongy substance including the medicament is formed which does not give off the active substance in one lot but releases it continuously by diffusion for absorption into the ambient medium. The mixture may further contain the conventional substances used in the manufacture of capsules, which impart consistency to the mixture or improve its slidability in the capsule-making machines, such as finely dispersed silicon dioxide, lecithin, phosphates and talcum (magnesium silicate). The gelatin shell of the capsule may be adjusted to normal solubility or it may be tanned, for example by treatment with formalin. In the latter case the diffusion of the medicament out of the spongy vehicle is further retarded.

Furthermore, the depot mixtures may contain substances that control the release of the active substances, for example phosphates, lactose, acids, bases, buffers, polyethylene, substances that form slimes or gels, such as carboxymethylcellulose and its salts, methylcellulose, alginic acid and alginates, gel-forming polymeric acrylic acid derivatives,

carboxy-vinyl polymers; substances that are insoluble in acid media but soluble in alkaline media, such as cellulose acetate-phthalate or finely dispersed silicon dioxide. These substances may also be soluble in the gastric juices as is dicalcium phosphate, so that they accelerate the release of the active substance, especially within the first hour after administration. Once the depot substance has entered the medium of the gastro-intestinal tract, the dicalcium phosphate is no longer dissolved so that the release of the medicament is slowed down. In this manner a relatively rapid release of an initial dose is achieved, and the remainder of the active substance is released more slowly. When a substance which forms a slime or gel is added to the depot material it swells up, thus causing the pores of the depot substance to enlarge and allowing less soluble active substances to be released more easily from the depot material. The substance added thus acts as a release controlling agent.

Suitable vehicles are

(a) liquid, water-soluble or water-miscible substances that can be filled into gelatin capsules and are stable in them, such as polyethyleneglycols, dioxolans, glycerolformal and glycofurol; liquid water-soluble or water-miscible alcohols, esters, acidamides or ethers;

(b) substances which form with water solutions, suspensions, emulsions or gels on addition of suitable emulsifiers, solubilizers or auxiliary solvents (other substances that promote miscibility with water), such as oils, fatty or waxy substances. Examples of such substance/emulsifier or auxiliary solvent mixtures are:

Arachis oil + polyhydroxyethylated castor oil,

neutral oils (triglycerides of fatty acids of medium chain length) + polyhydroxyethylene sorbitan monooleate,

castor oil + ethanol,

castor oil + polyethyleneglycol 400,

petrolatum + sorbitan trioleate,

petrolatum + polyhydroxyethylene sorbitan monooleate,

hardened arachis oil + polyhydroxyethylated castor oil.

These combinations may be extended or combined with each other to suit the above definition and the purpose in hand.

As actual sponge-forming substances there are suitable physiologically inert natural or synthetically produced substances which remain sufficiently long undissolved in water or in the gastric juices of the gastro-intestinal tract, such as polyvinyl ester, polyvinyl ether, polyvinylidene ester, polyvinylidene ether, polyvinyl and polyvinylidene acetals, polyvinylchloride, polyvinylidene chloride, polycarbonate, polyethylene, styrene + maleic anhydride copolymers, polyethylene + maleic anhydride copolymers alkyl-, alkenyl- and alkinyl-maleic anhydride copolymers, polystyrene, simple or mixed cellulose ethers and esters, polyacrylic acid, polymethacrylic acid, polyterephthalic acid, natural vegetable or animal or synthetic waxes and resins, montan waxes, gums, shellac, silicone resins and fats, fats, higher fatty acids and their salts, higher alcohols and their esters, as well as mixtures of the materials mentioned above.

The encapsulated active substances are continuously released from the capsules by diffusion from the microporous spongy body, independently of the prevailing pH value of the gastric juices and independently of the enzymatic conditions within the gastro-intestinal tract.

The medicament contained in the depot preparations of this invention is released to the ambient medium as follows: 1 hour after administration or the beginning of the test about 25%; after 3 hours about 50%; after 6 hours about 60%; after 8 hours about 75% and after 10 hours about 100%. Thus, the preparations of this invention satisfy the conditions to be fulfilled by up-to-date depot preparations.

The following Examples illustrate the invention. In each case the natural or synthetic substance forming the depot body is dissolved or suspended in the vehicle medium, and the active substance is then added. The filling thus prepared is then charged into gelatin capsules in known manner. The function of each of the ingredients is indicated as follows:

(A)=active ingredient; (B)=buffer; (E)=oil/water emulsifier; (S)=sponge-former; (V)=vehicle; (W)=swelling disintegrant and (X)=auxiliary solvent.

EXAMPLE 1

700 g of polyethyleneglycol 400 (V)
300 g of polyvinylacetate (S)
100 g of ephedrine . HCl (A)

EXAMPLE 2

600 g of 2-dimethyl-4-hydroxymethyl-1,3-dioxolan (V)
400 g of polyvinyl+maleic anhydride copolymer (S)
850 g of ethyl lactate (X)
50 g of ethanol (X)
100 g of procain . HCl (A)

EXAMPLE 3

700 g of 2-dimethyl-4-hydroxymethyl-1,3-dioxolan (V)
100 g of ethylcellulose (S)
100 g of styrene+maleic anhydride copolymer (S)
100 g of ethanol (X)
100 g of caffein (A)

EXAMPLE 4

900 g of polyethyleneglycol 300 (V)
200 g of shellac (S)

50 g of codein (A)
100 g of mucic acid (B)
50 g of dicalcium phosphate (B)
10 g of sodium carboxymethylcellulose (W)

EXAMPLE 5

800 g of triglyceride mixture (neutral oil) (V)
100 g of polyhydroxyethylated castor oil (E)
100 g of ethylcellulose (S)
50 g of ethanol (X)
50 g of pentobarbital (A)

EXAMPLE 6

100 g of polyvinylbutyl ether (S)
800 g of paraffinum perliquidum DAB 6, 3rd supplement (V)
100 g of sorbitan monooleate (E)
100 g of polyhydroxyethylene sorbitan monooleate (E)
200 g of extractum crataegi e fruct. (A)

EXAMPLE 7

100 g of polymethacrylic acid ester (S)
600 g of polyglycol 300 (V)
100 g of aluminium stearate (E)
50 g of ethylpapaverine (A)

EXAMPLE 8

200 g of styrene+maleic anhydride co-polymer (S)
700 g of 2-dimethyl-4-hydroxymethyl-1,3-dioxolan (V)
100 g of ethanol (X)
100 g of aminophenazone (A)

EXAMPLE 9

100 g of zein (W)
300 g of polyethyleneglycol 400 (V)
100 g of shellac (S)
100 g of polymethacrylic acid derivative (S)
2 g of cellulose acetate-phthalate (S)
50 g of oxeladine citrate (A)

EXAMPLE 10

900 g of polyethyleneglycol 300 (V)
100 g of polyvinyl isobutyl ether (S)
200 g of shellac (S)
100 g of phthalicacid (B)
50 g of dicalcium phosphate (B)
20 g of finely dispersed silicon dioxide (B)
20 g of chlorophenamine maleate (A)

In the following Example the solid substances were melted by heating and intimately mixed. Then the active substance was admixed and the warm, liquid mass filled into capsules.

EXAMPLE 11

900 g of polyethyleneglycol 4000 (V)
100 g of polyethyleneglycol 400 (V)
100 g of beeswax DAB 6 (S)
100 g of polyhydroxyethylated castor oil (E)
100 g of shellac (S)
150 g of pyrilamine maleate (A)

WHAT WE CLAIM IS:—

1. A gelatin capsule containing a depot medicament, the depot medicament comprising a solution or suspension, which solution or suspension is liquid or flowable at room temperature, of one or more physiologically active substances and one or more substances selected from physiologically inert natural substances and physiologically inert synthetic substances, which physiologically inert substances are also inert to gelatin and are insoluble or only gradually soluble in water or in the juices of the gastro-intestinal tract, in a liquid vehicle, which vehicle comprises a liquid water-miscible substance and/or a liquid mixture of a water-immiscible substance with a water-oil emulsifier or an auxiliary solvent, each of the physiologically inert natural or synthetic substances being such that, together with the liquid vehicle, it forms a microporous spongy body when it comes into contact with water or with the juice of the gastrointestinal tract.

2. A capsule as claimed in claim 1, wherein the or one of the physiologically inert synthetic substances is a polyvinyl homopolymer or copolymer.

3. A capsule as claimed in claim 1, wherein the or one of the physiologically inert synthetic substances is a cellulose ether.

4. A capsule as claimed in claim 1, wherein the or one of the physiologically inert natural substances is shellac.

5. A capsule as claimed in any one of claims 1 to 4, wherein the depot medicament contains one or more substances mentioned herein that control the release of the active substance(s).

6. A capsule as claimed in claim 5, wherein the or one of the substances that control the release of the active substance(s) is dicalcium phosphate.

7. A capsule as claimed in any one of claims 1 to 6, wherein the gelatin of the capsule has been tanned by a formulain treatment.

8. A capsule as claimed in claim 1 and described herein.

9. A gelatin capsule containing a depot medicament as described in any one of the Examples.

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